



eLITERATURE REVIEW

eInfections Review

Presented by
The Johns Hopkins University
School of Medicine

Supported by an Educational
Grant from AstraZeneca,
Cubist Pharmaceuticals and
ViroPharma, Inc.



[HOME](#) [CME INFORMATION](#) [PROGRAM DIRECTORS](#) [NEWSLETTER ARCHIVE](#) [EDIT PROFILE](#) [RECOMMEND TO A COLLEAGUE](#)

Welcome to Volume 2 of eInfections Review

With the launch of this issue, we want to welcome back our returning subscribers, say hello to our newly registered clinicians, and thank the more than 1500 of you receiving this issue and for your involvement in this program. In volume 2, we'll continue to provide you with current, clinically relevant data on topics important to helping you improve outcomes for your patients. The topics will be delivered bi-monthly: 6 bi-monthly newsletters and 6 featured podcast cases of the month. Topics will include: H1N1, Vancomycin and MRSA, Osteomyelitis/Diabetic Foot Infections, and others.

November 2009: VOLUME 2, NUMBER 1

Pandemic and Seasonal Influenza

In this Issue...

Influenza has become the most pressing public health problem worldwide with the emergence of pandemic H1N1 influenza A virus. Although the virus appears to cause mild infection in most individuals, severe illness has been reported in children, pregnant women, and nonelderly adults with comorbidities. Significant efforts have focused on producing a novel H1N1 influenza A vaccine, in an attempt to blunt the impact of this new virus on a largely nonimmune population.

In this issue, key developments acquired from the early case series of novel H1N1 influenza will be reviewed in the context of how diagnosis, treatment, and vaccination recommendations have been shaped.



Program Information

[CME Info](#)
[Accreditation](#)
[Credit Designations](#)
[Intended Audience](#)
[Learning Objectives](#)
[Internet CME Policy](#)
[Faculty Disclosures](#)
[Disclaimer Statement](#)

Length of Activity

1 hour

Release Date

November 3, 2009

Expiration Date

November 2, 2011

Next Issue

December 1, 2009

COMPLETE THE POST-TEST

Step 1.
Review the CE Information and study the educational content.

Step 2.
Click the post-test link at the end of the newsletter.

Step 3.
Follow the instructions to access a post-test.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Discuss which patient populations are at greater risk for pandemic H1N1 influenza A
- Describe the advantages of molecular diagnosis of the novel H1N1 influenza A virus, as well as the limitations of conventional and rapid testing methodologies.
- Evaluate treatment and vaccination recommendations in the context of both pandemic influenza as well as seasonal influenza.

IMPORTANT CME INFORMATION

▼ Program Begins Below

ACCREDITATION STATEMENTS

The Johns Hopkins University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATIONS

Physicians

eNewsletter: The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

INTERNET CME/CNE/CPE POLICY

The Office of Continuing Medical Education (CME) at The Johns Hopkins University School of Medicine is committed to protect the privacy of its members and customers. The Johns Hopkins University SOM CME maintains its Internet site as an information resource and service for physicians, other health professionals and the public.

Continuing Medical Education at The Johns Hopkins University School of Medicine will keep your personal and credit information confidential when you participate in a CME Internet based program. Your

Podcast: The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 0.5 *AMA PRA Category 1 Credit(s)*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

DISCLAIMER STATEMENT

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. Use of The Johns Hopkins University School of Medicine name implies review of educational format design and approach. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings and adverse effects before administering pharmacologic therapy to patients.

SUCCESSFUL COMPLETION

To successfully complete this activity, participants must read the content, link to [The Johns Hopkins University School of Medicine's CME website](#), complete the post-test, and evaluation. Once you receive a passing grade, you can access and print your certificate of credit. NOTE: If you have already registered for the Hopkins CME programs at the CME Website simply enter the requested information when prompted.

STATEMENT OF RESPONSIBILITY

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

INTENDED AUDIENCE

This activity has been developed for the Primary Care Physician, Internist, and Infectious Disease Specialist.

There are no prerequisites.

information will never be given to anyone outside of The Johns Hopkins University School of Medicine's CME program. CME collects only the information necessary to provide you with the services that you request.

FACULTY DISCLOSURE

As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of Johns Hopkins University School of Medicine to require the disclosure of the existence of any relevant financial interest or any other relationship a faculty member or a provider has with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following.

- **Paul G. Auwaerter, MD** – has disclosed that he has served as a consultant Adamas Pharmaceuticals, LifeCell, Schering-Plough, and Wyeth. He has disclosed that he is a stock shareholder of Johnson & Johnson, Merck and Pfizer.
- **John G. Bartlett, MD** – has disclosed that he has served as a consultant for Salient.
- **Sara E. Cosgrove, MD, MS** – has disclosed that she has received grants or research support from Cubist, AdvanDX, and Astellas, and served as a consultant for Theravance/Astellas, Merck, and Forest.

[Guest Author's Disclosures](#)

HARDWARE & SOFTWARE REQUIREMENTS

Pentium 800 processor or greater, Windows 98/NT/2000/XP or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K Modem or better, Windows Media Player 9.0 or later, 128 MB of RAM, monitor settings: high color at 800 x 600 pixels, sound card and speakers, Adobe Acrobat Reader.

THIS ISSUE

- [COMMENTARY from our Guest Author](#)
- [NOTES FROM THE EPICENTER OF PANDEMIC H1N1 INFLUENZA: MEXICO SPRING 2009](#)
- [CAN SCIENCE FORECAST INFLUENZA EPIDEMICS?](#)
- [PANDEMIC H1N1 INFLUENZA A: UNITED STATES AND NEW ZEALAND EXPERIENCES](#)
- [DIAGNOSTIC TESTING OF NOVEL H1N1 INFLUENZA A](#)

Course Directors

Paul G. Auwaerter, MD

Associate Professor of Medicine
Clinical Director,
Division of Infectious Diseases and
General Internal Medicine
The Johns Hopkins University
School of Medicine
Baltimore, MD

John G. Bartlett, MD

Professor of Medicine
Department of Medicine
The Johns Hopkins University
School of Medicine
Baltimore, MD

Sara E. Cosgrove, MD, MS

Assistant Professor of Medicine
Division of Infectious Diseases
Director, Antibiotic Management
Program
Associate Hospital Epidemiologist
The Johns Hopkins University
School of Medicine
Baltimore, MD

GUEST AUTHOR OF THE MONTH

Commentary & Reviews:



Paul Auwaerter, MD

Associate Professor of Medicine
Clinical Director,
Divisions of Infectious Diseases and General Internal Medicine
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Guest Faculty Disclosures

Paul G. Auwaerter, MD, has disclosed that he has served as a consultant for Adamas Pharmaceuticals, Schering-Plough and Wyeth. He has also disclosed that he is a stock shareholder for Johnson and Johnson, Merck, and Pfizer.

Unlabeled/Unapproved Uses

The authors have indicated that there will be no reference to unlabeled/unapproved uses of drugs or products in the presentation.

[Program Directors' Disclosures](#)

COMMENTARY

Influenza has earned heightened attention this year with the emergence of the novel H1N1 influenza A virus. Reports from the initial outbreak in Mexico showed an association with severe lung infection.¹ As this strain has spread globally, it appears that most people who acquire this infection have a mild respiratory illness; however, swine-origin H1N1 strains have not circulated widely since 1957, so substantial numbers of individuals have no immunity, which has led to >300,000 confirmed cases being reported to the World Health Organization (WHO).^{2,3} As a result, WHO has declared an influenza pandemic—the first since 1968—with more than 191 countries reporting confirmed human infections within 6 months of the first identified human infection.⁴ The actual number of cases is unknown and is far higher, as most infections are not subject to diagnostic evaluation and the WHO has ceased active monitoring.

Prior to the onset of the novel H1N1 pandemic, emerging issues regarding seasonal influenza focused on 2 major themes: childhood immunization and the rapid spread of oseltamivir-resistant virus. To place the ongoing pandemic in some context, based on averages from the years 1979 through 2001, seasonal influenza has accounted for approximately 36,000 deaths and 226,000 hospitalizations annually in the United States.^{5,6} These numbers generally have been steady, despite efforts at enhancing rates of immunization among the highest risk groups, including the elderly and those with comorbidities.⁷ New recommendations to vaccinate all school-aged children have been driven by studies documenting that this population typically has the highest attack rates of influenza. Therefore, targeted efforts toward achieving universal influenza immunization among children may reduce the rates of infection in households and possibly in the larger community as well.⁸⁻¹³ It is currently recommended that all children from 6 months through 18 years of age receive influenza immunization annually. This new recommendation seeks to raise overall immunization rates in children, which most recently have been estimated to be about 40% in the 2- to 4-year-old age-group and approximately 20% in the 5- to 17-year-old age-group (based on 2007 to 2008 data).¹⁴ Achieving immunization rates of >70% to 80% will likely take a few years to implement, but may be among the most effective measures for reducing the impact of influenza in all populations.

One of the surprises from the 2007 to 2008 influenza season was the rapid emergence of oseltamivir resistance in seasonal H1N1 (nonpandemic) influenza A virus. By July 2009, about 99% of these seasonal viruses displayed oseltamivir resistance but remained susceptible to the amantadines and to zanamivir.^{9,15} Interestingly, this resistance to the



most frequently used antiviral neuraminidase inhibitor appeared to emerge in Scandinavia, where antiviral agents are infrequently used, rather than in a country such as Japan, which has one of the highest per capita uses of these agents.

Currently, interim recommendations from the Centers for Disease Control and Prevention (CDC) emphasize that antiviral therapy should be directed toward patients hospitalized with influenza or those at highest risk for developing complications of influenza.¹⁶ It is predicted that novel H1N1 will be the predominant circulating virus for 2009 to 2010, and this strain appears susceptible to such neuraminidase inhibitors as oseltamivir and zanamivir. Whether seasonal influenza strains with oseltamivir resistance will circulate widely in the forthcoming season is unknown; however, routine use of amantadines is not currently suggested in combination with neuraminidase inhibitors for empiric treatment of influenza because the majority of strains currently circulating in the fall of 2009 are novel H1N1 (see seasonal influenza recommendations below).

Current 2009 guidelines for the treatment of influenza include the following¹⁶:

- Most healthy people who have an influenza-like illness do not require antiviral medications
- Most healthy people with exposure to individuals with an influenza-like illness or confirmed influenza do not require prophylaxis
- If severe illness develops, including lower respiratory tract infection or serious clinical deterioration, then empiric antiviral therapy should be initiated promptly, regardless of a person's health status or age
- Treatment with either oseltamivir or zanamivir is recommended for all persons with suspected or confirmed influenza requiring hospitalization

Early empiric treatment with oseltamivir or zanamivir should be considered for individuals with suspected or confirmed influenza who are at higher risk for complications, including:

- Children <2 years of age
- Persons ≥65 years
- Pregnant women
- Persons of any age with certain chronic medical or immunosuppressive conditions
- Persons <19 years of age who are receiving long-term aspirin therapy

It is worth noting that the common understanding of administering oseltamivir only within the first 48 hours of symptom onset in order to yield efficacy was based on a randomized, controlled placebo trial in basically healthy and ambulatory populations.¹⁷ For the more severely ill or hospitalized patient, there is growing evidence that neuraminidase inhibitor treatment is beneficial, regardless of timing.¹⁸⁻²⁰

The first description of oseltamivir-resistant pandemic H1N1 influenza virus was in 2 patients who were both immunosuppressed and received treatment with oseltamivir, with documented prolonged viral shedding.²¹ The oseltamivir-resistant mutation does not render this virus resistant to zanamivir, so this inhaled neuraminidase inhibitor would be the treatment of choice. A more recent report has documented emergence of oseltamivir resistance in children who received oseltamivir prophylaxis while at summer camp.²² Some have worried that resistance may more commonly arise if lower doses of oseltamivir are used, as with prophylaxis dosing, or if the agent is widely used for nonserious illness. These reports have led public health authorities to recommend against the routine use of oseltamivir for either prophylaxis or treatment, in part to prevent emergence and spread of resistant virus, as well as to reserve the drug for those most in need. To date, no evidence of widespread oseltamivir-resistant novel H1N1 virus has been reported.

Regarding influenza immunization, in addition to the existing recommendations for seasonal influenza, production of the novel H1N1-based vaccines will be also recommended, with initial groups targeted at those who are at the highest risk (see below).²³ Children appear to be among the highest-risk groups for novel H1N1 influenza based on experience to date, while older adults make up a much smaller than usual

case number than for seasonal influenza. This phenomenon in adults over 65 may be due to some immunity that could be based on exposure to circulating H1N1 viruses prior to 1957, but not from prior immunization with seasonal influenza vaccines.^{3,24}

Preliminary information from clinical trials suggests that the vaccine may be potent enough to produce sufficient immunity after 1 dose in adults and children > 10 years of age, whereas younger children will likely require 2 doses.²⁵ Although an adjuvant-based vaccine has shown evidence of sufficient immunity within 2 weeks of administration, this vaccine will not likely be used in the United States.²⁶ Development and delivery of a new influenza vaccine in a short time represent significant achievements, although the logistical hurdles of immunizing an estimated 159 million Americans for whom the vaccine has been initially recommended loom large. Since the novel H1N1 influenza has been mild thus far, the urgency may be less than initially believed from the first reports from Mexico. The eventual response to both vaccine production and delivery in the fall and the winter of 2009 to 2010 will be highly informative, and lessons learned will hopefully direct further improvements to ready the public health system, especially if a more virulent influenza strain develops.

Initial groups recommended to receive the novel H1N1 vaccine include the following²³:

- Pregnant women
- Persons who live with or provide care for infants <6 months of age
- Health care and emergency medical services personnel
- Individuals 6 months to 24 years of age
- Individuals 25 to 64 years of age who have medical conditions (e.g., asthma, hypertension, diabetes, HIV) that increase the risk for influenza-related complications

If the vaccine supply does not meet the targeted demand, the CDC has further refined recommendations to prioritize the following populations²³:

- Pregnant women
- Persons who live with or provide care for infants <6 months of age
- Health care and emergency medical services personnel who have direct contact with patients or infectious material
- Children 6 months to 4 years of age
- Children and adolescents 5 to 18 years of age who have medical conditions that increase the risk for influenza-related complications

Principal Changes for Seasonal Influenza: 2009–2010⁹

1. Annual vaccination of all children aged 6 months–18 years

Annual vaccination of all children aged 6 months–4 years (59 months) and older children with conditions that place them at increased risk for complications from influenza should continue to be a primary focus of vaccination efforts as providers and programs transition to routinely vaccinating all children.

2. Most seasonal influenza A (H1N1) virus strains are resistant to oseltamivir

Treatment and prophylaxis recommendations may change as information on circulating strains. Interim recommendations are available:
<http://www.cdc.gov/h1n1/recommendations.htm>

A number of important scientific and clinical papers have quickly analyzed the novel H1N1 influenza A pandemic. As more than 40 years have elapsed since global spread of a new influenza virus, this literature review will focus on some of the studies that have guided clinicians, public health authorities, and scientists.

Commentary References

1. Chowell G, Bertozzi SM, Colchero MA, Lopez-Gatell H, Alpuche-Aranda C, et al. [Severe respiratory disease concurrent with the circulation of H1N1 influenza](#). *N Engl J Med*. 2009;361(7):674-679.
2. Centers for Disease Control and Prevention (CDC). [Serum cross-reactive antibody response to a novel influenza A \(H1N1\) virus after vaccination with seasonal influenza vaccine](#). *Morb Mortal Wkly Rep*. 2009;58(19):521-524.
3. Hancock K, Vequilla V, Lu X, Zhong W, Butler EN, et al. [Cross-Reactive Antibody Responses to the 2009 Pandemic H1N1 Influenza Virus](#). *N Engl J Med*. 2009 Sep 10 [Epub ahead of print].
4. [World Health Organization. Pandemic \(H1N1\) 2009 - update 67](#).
5. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, et al. [Mortality associated with influenza and respiratory syncytial virus in the United States](#). *JAMA*. 2003;289(2):179-186.
6. Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, et al. [Influenza-associated hospitalizations in the United States](#). *JAMA*. 2004;292(11):1333-1340.
7. Nichol KL, Treanor JJ. [Vaccines for seasonal and pandemic influenza](#). *J Infect Dis*. 2006;194 (Suppl 2):S111-118.
8. Glezen WP. [Benefits of a universal influenza immunization program: more than the reduction in the use of antibiotics](#). *Clin Infect Dis*. 2009;49(5):757-758.
9. Fiore AE, Shay DK, Broder K, Iskander JK, Uyeki TM, et al; Centers for Disease Control and Prevention (CDC). [Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices \(ACIP\), 2009](#). *MMWR Recomm Rep*. 2009; 58(RR-8):1-52
10. Kwong JC, Stukel TA, Lim J, McGeer AJ, Upshur RE, et al. [The effect of universal influenza immunization on mortality and health care use](#). *PLoS Med*. 2008;5(10):e211
11. Ghendon YZ, Kaira AN, Elshina GA. [The effect of mass influenza immunization in children on the morbidity of the unvaccinated elderly](#). *Epidemiol Infect*. 2006;134(1):71-78
12. Kwong JC, Maaten S, Upshur RE, Patrick DM, Marra F. [The effect of universal influenza immunization on antibiotic prescriptions: an ecological study](#). *Clin Infect Dis*. 2009;49(5):750-756.
13. Moran K, Maaten S, Guttman A, Northrup D, Kwong JC. [Influenza vaccination rates in Ontario children: implications for universal childhood vaccination policy](#). *Vaccine*. 2009;27(17):2350-2355.
14. Centers for Disease Control and Prevention. [2009-10 Influenza Prevention & Control Recommendations: Influenza Vaccination Coverage Levels](#). Accessed October 9, 2009
15. Meijer A, Lackenby A, Hungnes O, Lina B, van-der-Werf S, et al. [Oseltamivir-resistant influenza virus A \(H1N1\), Europe, 2007-08 season](#). *Emerg Infect Dis*. 2009;15(4):552-560.
16. Centers for Disease Control and Prevention. [Updated Interim Recommendations for the Use of Antiviral Medications in the Treatment and Prevention of Influenza for the 2009-2010 Season](#). Accessed October 9, 2009.
17. Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, et al. [Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial.US Oral Neuraminidase Study Group](#). *JAMA*. 2000;283:1016-1024
18. Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG, et al; Expert Panel of the Infectious Diseases Society of America. [Seasonal influenza in adults and children--diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America](#). *Clin Infect Dis*. 2009;48(8):1003-1032
19. McGeer A, Green KA, Plevneshi A, Shigayeva A, Siddiqi N, Raboud J, Low DE; Toronto Invasive Bacterial Diseases Network. [Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada](#). *Clin Infect Dis*. 2007;45(12):1568-1575
20. McGeer AJ. [Diagnostic testing or empirical therapy for patients hospitalized with suspected influenza: what to do?](#) *Clin Infect Dis*. 2009;4(Suppl 1):S14-19
21. Centers for Disease Control and Prevention (CDC). [Oseltamivir-resistant novel influenza A \(H1N1\) virus infection in two immunosuppressed patients - Seattle, Washington, 2009](#). *MMWR Morb Mortal Wkly Rep*. 2009;58(32):893-896.
22. Centers for Disease Control and Prevention (CDC). [Oseltamivir-resistant 2009 pandemic influenza A \(H1N1\) virus infection in two summer campers receiving prophylaxis--North Carolina, 2009](#). *MMWR Morb Mortal Wkly Rep*. 2009;58(35):969-972.
23. National Center for Immunization and Respiratory Disease, Centers for Disease Control and Prevention (CDC). [Use of influenza A \(H1N1\) 2009 monovalent vaccine: recommendations of the Advisory Committee on Immunization Practices \(ACIP\), 2009](#). *MMWR Recomm Rep*. 2009; 58(RR-10):1-8.

24. Centers for Disease Control and Prevention (CDC). [Serum cross-reactive antibody response to a novel influenza A \(H1N1\) virus after vaccination with seasonal influenza vaccine.](#) *MMWR Morb Mortal Wkly Rep.* 2009;58(19):521-524.
25. Greenberg ME, Lai MH, Hartel GF, Wichems CH, Gittleson C, Bennet J, et al. [Response after One Dose of a Monovalent Influenza A \(H1N1\) 2009 Vaccine -- Preliminary Report.](#) *N Engl J Med.* 2009; 361 (11).
26. Clark TW, Pareek M, Hoschler K, Dillon H, Nicholson KG, Groth N, et al. [Trial of Influenza A \(H1N1\) 2009 Monovalent MF59-Adjuvanted Vaccine — Preliminary Report.](#) *N Engl J Med.* 2009;361(11).

NOTES FROM THE EPICENTER OF PANDEMIC H1N1 INFLUENZA: MEXICO SPRING 2009

Chowell G, Bertozzi SM, Colchero MA, Lopez-Gatell H, Alpuche-Aranda C, et al. **Severe respiratory disease concurrent with the circulation of H1N1 influenza.** *N Engl J Med.* 2009;361(7):674-679.

(For non-journal subscribers, an additional fee may apply for full text articles.)



[View journal abstract](#)



[View full article](#)

This report by Chowell and associates discusses why high-level concern across the globe was triggered by evidence of serious pulmonary infection associated with the H1N1 influenza virus in Mexico. Data from the outbreak offered one of the first glimpses into patient presentations and mortality rates, allowing insight into the behavior of this virus. This study focused on the epicenter of what was to become the pandemic, with an analysis of 2155 cases of severe pneumonia that involved 821 hospitalizations and 100 deaths. The authors compared the current experience with earlier eras of seasonal influenza [see table 1].

Most importantly, a significant shift was noted in the age of affected patients. Historically, the 5- to 59-year-old age-group accounts for 17% of seasonal influenza deaths and 32% of total cases. During the late March through April 2009 time frame, when these new cases were analyzed, influenza-related mortality in this younger age- group rose considerably, accounting for 87% of deaths and 71% of all cases. For the 20- to 24-year-old age-group with severe pneumonia, the mortality rate was 13%, compared with 15% in the 35- to 39-year-old age-group.

The key information gained is that this novel H1N1 influenza A virus follows 2 patterns observed in earlier pandemics: (1) occurring off the traditional peak of the influenza season; and (2) affecting a younger population, which is similar to what occurred in the 1918 influenza pandemic. Mortality, which was historically typically highest in the 80+ age group (42%) from seasonal influenza was instead among the lowest in the elderly population in Mexico City, at 3% [Table 1]. These data were the first to suggest that people born prior to 1957 may have been exposed to the H1N1 strains that were in circulation then and may therefore still harbor some amnesic immune response that affords some protection.

 RECOMMEND TO
A COLLEAGUE

 NEWSLETTER
ARCHIVE

Table 1. Proportion of Mortality from Severe Pneumonia According to Age Group during the 2009 Study Period, as Compared with Influenza Seasons from 2006 through 2008, in Mexico.*

Age Group (year)	Mortality (percent)		
	2006–2008 Influenza seasons	March 24 to April 29, 2009	Ratio, Study Period to Referent Period
0–4	17	5	0.3
5–9	1	5	7.6
10–14	1	6	10.7
15–19	1	7	8.6
20–24	1	13	11.7
25–29	1	11	10.3
30–34	1	9	6.0
35–39	2	15	9.4
40–44	2	9	4.8
45–49	2	5	2.1
50–54	2	4	1.6
55–59	3	3	1.2
60–64	3	0	0.0
65–69	5	1	0.2
70–74	7	2	0.3
75–79	9	2	0.2
≥80	42	3	0.1

*Data were reported by the National System of Health Care Information and the National Epidemiological Surveillance System (SINAVE).

A companion report focused on 18 confirmed cases of novel H1N1 pneumonia that required hospitalization in Mexico City. The majority of the patients were between the ages of 13 and 47, and most also had no preexisting medical conditions that would otherwise predispose them to severe influenza infection.¹ This study highlighted the fact that the patients had a patchy bilateral pneumonia that resembled acute respiratory distress syndrome and appeared to be solely due to the virus, with no evidence of secondary bacterial infection. Of the 8 patients who died, 7 had multi-organ system failure. This was of considerable interest, since some experts believe that the reason for high mortality in the 1918 influenza pandemic was secondary bacterial pneumonia.²⁻⁴ Why previously healthy people died of influenza in this fashion is unclear, but possible explanations include induction of intense cytokine activity causing severe inflammation or co-infection with an as-of-yet-undetected pathogen.

These 2 reports are based on clinical information that truly raised eyebrows in April and May of 2009, with concerns that this could represent the next virulent 1918-style pandemic. As more clinical experience amassed with the spread of the virus, in general, this form of influenza was believed to be similar or even milder than seasonal influenza.

References

1. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, Hernandez M, Quiñones-Falconi F, Bautista E, et al; INER Working Group on Influenza. [Pneumonia and respiratory failure from swine-origin influenza A \(H1N1\) in Mexico.](#) *N Engl J Med.* 2009;361(7):680-689.

2. Fedson DS. [Was bacterial pneumonia the predominant cause of death in the 1918-1919 influenza pandemic?](#) *J Infect Dis.* 2009;199(9):1408-1409; author reply 1409-1410.
3. Klugman KP, Astley CM, Lipsitch M. [Time from illness onset to death, 1918 influenza and pneumococcal pneumonia.](#) *Emerg Infect Dis.* 2009;15(2):346-347.
4. Brundage JF, Shanks GD. [Deaths from bacterial pneumonia during 1918-19 influenza pandemic.](#) *Emerg Infect Dis.* 2008;14(8):1193-1199.

CAN SCIENCE FORECAST INFLUENZA EPIDEMICS?

Fraser C, Donnelly CA, Cauchemez S, Hanage WP, Van Kerkhove MD, Hollingsworth TD, et al; WHO Rapid Pandemic Assessment Collaboration. **Pandemic potential of a strain of influenza A (H1N1): early findings.** *Science.* 2009;324(5934):1557-1561.

(For non-journal subscribers, an additional fee may apply for full text articles.)



[View journal abstract](#)



[View full article](#)

Fraser and colleagues used mathematical modeling to determine how likely and with what speed a new virus might spread, using estimates of viral reproduction values based on an infection entering a virgin population, in this case using the 23,000 influenza cases reported in La Gloria, Mexico, by late April 2009. If such modeling were accurate, it could prove invaluable to public health authorities, similar to how the improvement in predictions of hurricane paths over the last few decades has allowed public officials to issue warnings on hurricane landfall based on calculations that are seldom wrong.

Since influenza viruses vary in genetic composition, any stable determination of actual transmission rates will be difficult. A viral reproduction or transmissibility (R_0) rate, which reflects the average number of secondary cases of infection caused by a usual primary case in a susceptible population, is one of the critical values providing guidance on the potential for an epidemic. As an example, an R_0 of 1.0 would reflect no transmission. If the R_0 were >1.0 , an epidemic will occur, and if the R_0 were <1.0 , then an outbreak should subside. An R_0 of >2.0 for a novel pathogen is thought to correlate with a high probability of a severe epidemic. The R_0 rate will vary depending on specific situations—for example, it will be higher in household settings than in schools or day-care locations, and lowest in the general community.

R_0 estimates have varied in different studies of the 1918 pandemic strain, ranging from 1.8 to 4.0, with 2.0 to 3.0 being among the most commonly determined values.¹ To offer some perspective, severe acute respiratory syndrome (SARS) had an R_0 estimate of 3 (excluding superspreaders), measles has an R_0 of 10 to 15, and other values are as high as 16 to 18 for pertussis and 8 to 12 for polio.

Using data from the initial reports from Mexico, the authors estimated the R_0 for novel H1N1 influenza A to be between 1.4 and 1.6, incorporating a case fatality rate of 0.4%. How well has this forecast dating from May 2009 stood to date?

Many were geared for a predicted attack rate of 50% to 60%, based on examinations of the first waves of past influenza pandemics. More recent investigation, such as studying schools and households in the United States, have determined an attack rate of closer to 27.3% (95% confidence interval [CI], 12.2% to 50.5%), based on secondary transmission in US. households.² This group estimated an R_0 of 1.3 to 1.7, with a generation interval from index to secondary case infection of 2.6 to 3.2 days.

Since the early estimate from Fraser and coworkers appears to have been a reasonable estimate, the R_0 values could bolster arguments that extreme measures, such as quarantine, social distancing, or a mass antiviral campaign early on, may have aborted the spread beyond Mexico. Whether the genie can be kept in the bottle is less than clear, but R_0 values provide some guidance on whether this could be possible. Although H1N1



was not contained, for reasons that remain unclear, SARS (which had a higher R_0 value) was contained and did not spread with the numbers or the speed that has been witnessed with pandemic H1N1 influenza A.

This mathematical modeling based on generation time of the virus also estimated that the virus emerged as a human pathogen in January 2009, although it may have been as early as November 2008. The first documented human case occurred in a 10-year-old asthmatic child in San Diego, California, in March 2009.^{3 4}

This modeling has many other complexities and cautions that are beyond the scope of this review. One important factor is that cross-species recombinations or other changes in the virus during the course of the epidemic may further alter the R_0 if viral reassortment changes transmission characteristics.⁵ One use of this simulation model using an R_0 of 1.4 to 1.6 evaluated the potential effectiveness of a vaccine. The model suggested that coverage must reach 70% overall, beyond targeting high-risk groups and health care workers, in order to alleviate a severe epidemic.² This, of course, does not mean that individuals would not benefit from vaccine administration, but it does indicate that that ability to produce and to timely administer the vaccine to blunt the overall spread of the virus will be unlikely during this season, and may not have been worth the effort from the start, given the current capabilities.

Despite the potential importance of modeling, much as how economic forecasters fare in predicting changes in the economy or stock markets, these researchers highlight the fact that much uncertainty exists regarding how the virus will behave even in the short-term. Hence, these early analyses are currently of limited help but, with refinement, may become important tools for public health authorities and governments. What has been generally agreed on as the most helpful lesson learned to date has been the rapid release of information and engagement of public health resources across the globe by the Mexican government.³ The sharing and the cooperation seen early in this epidemic should be the model for the future.

References

1. Coburn BJ, Wagner BG, Blower S. [Modeling influenza epidemics and pandemics: insights into the future of swine flu \(H1N1\)](#). *BMC Med.* 2009;7:30.
2. Yang Y, Sugimoto JD, Halloran ME, Basta NE, Chao DL, Matrajt L, et al. [The Transmissibility and Control of Pandemic Influenza A \(H1N1\) Virus](#). *Science.* 2009 Sep 10. [Epub ahead of print].
3. Stern AM, Markel H. [What Mexico taught the world about pandemic influenza preparedness and community mitigation strategies](#). *JAMA.* 2009;302(11):1221-1222.
4. Centers for Disease Control and Prevention (CDC). [Swine influenza A \(H1N1\) infection in two children--Southern California, March-April 2009](#). *MMWR Morb Mortal Wkly Rep.* 2009;58(15):400-402.
5. McCaw JM, McVernon J, McBryde ES, Mathews JD. [Influenza: accounting for prior immunity](#). *Science.* 2009;325(5944):1071.

PANDEMIC H1N1 INFLUENZA A: UNITED STATES AND NEW ZEALAND EXPERIENCES

Centers for Disease Control and Prevention (CDC). **2009 pandemic influenza A (H1N1) virus infections - Chicago, Illinois, April-July 2009**. *MMWR Morb Mortal Wkly Rep.* 2009;58(33):913-918.

(For non-journal subscribers, an additional fee may apply for full text articles.)



[View journal abstract](#)



[View full article](#)



Centers for Disease Control and Prevention (CDC). **Surveillance for the 2009 pandemic influenza A (H1N1) virus and seasonal influenza viruses - New Zealand, 2009.** *MMWR Morb Mortal Wkly Rep.* 2009;58(33):918-921.

(For non-journal subscribers, an additional fee may apply for full text articles.)



[View journal abstract](#)



[View full article](#)

The first report from the CDC examined patients from the Chicago, Illinois, area with laboratory-confirmed cases of novel H1N1 from April 24 to July 25, providing one of the first glimpses into how this virus has been behaving in the United States population. A total of 1557 cases were included, with 1352 (87%) nonhospitalized and 205 (13%) requiring hospitalization.

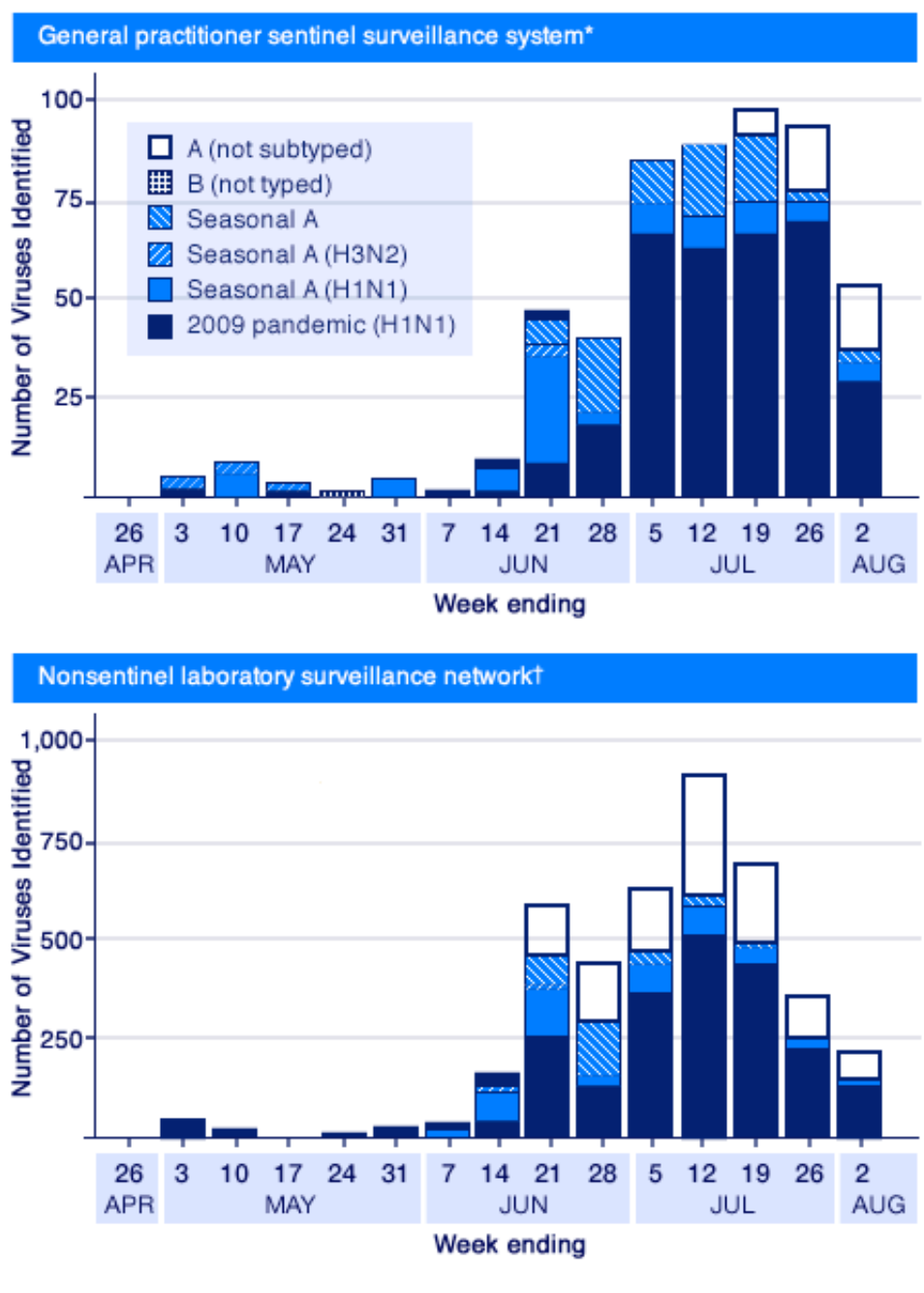
Age Group	Number (total = 1,557)	(%)	Attack rate/100,000
0-4	247	16	113
5-14	624	40	147
15-29	345	22	48
30-59	278	18	25
≥60	41	3	10

As illustrated in Table 1, these attack rates show that children are more than 14 times more likely to be infected than adults over the age of 60. Hospitalization rates were highest in the 0- to 4-year-old age-group, followed by the 5- to 14-year-old age-group. Of those hospitalized, 40 (20%) required treatment in the intensive care unit and 9 (4.4%) were placed on mechanical ventilation. The actual mortality rate was not estimated in this data set because of reporting issues, although as of late August, 7 deaths due to novel H1N1 virus were confirmed in this Chicago population—most of whom had comorbidities, including pregnancy, malignancies, end-stage renal disease, obesity, and asthma. All individuals appeared to succumb to respiratory complications. This study is limited, since the number of actual cases is likely underestimated as the number of confirmed cases is no doubt lower.

This skewing toward younger populations was described in the early data from Mexico and is also representative of some influenza pandemics. This U.S.-based information reinforces the recommendation that children be among the first priority groups to receive the pandemic H1N1 vaccine when it becomes available.

Although pandemic H1N1 emerged in the Northern Hemisphere first in the spring of 2009, it appeared in the Southern Hemisphere just thereafter, in the midst of their usual wintertime respiratory viral season. The second CDC report examines how the virus behaved in New Zealand.

Figure 1. Number of Influenza viruses identified by type — New Zealand, week ending May 3 through week ending August 2, 2009



*527 influenza viruses identified by 95 general practitioners, representing all 24 health districts, with a combined patient population of 409,044, approximately 9.6% of the New Zealand population.

†3,931 influenza viruses identified by the National Influenza Center at the Institute of Environmental Science and Research, plus hospital laboratories at Auckland, Waikato, Wellington and Christchurch.

As shown in Figure 1, novel H1N1 virus rapidly replaced seasonal influenza virus as the predominant isolate in New Zealand. Total activity overall for influenza-like illnesses was approximately 3 times the peak weekly incidence compared with the same 2008 period. By early July 2009, 80% of viruses in the sentinel surveillance group were due to the 2009 pandemic H1N1 influenza virus.

Of some interest, New Zealand authorities were aware of the likely original importation of pandemic influenza A (H1N1) that occurred in April when high school students returned from a trip to Mexico. Initially, the government attempted rigorous containment and screening measures, which included isolation of these index cases and quarantine of their contacts, along with oseltamivir therapy and screening of incoming airline passengers. Although this may have delayed the frequency of developing cases, it clearly was insufficient to prevent spread of the virus.

The New Zealand experience is often pointed to as what will likely happen in the United States: the pandemic strain, as opposed to usual seasonal influenza viruses, will cause most influenza illnesses.

DIAGNOSTIC TESTING OF NOVEL H1N1 INFLUENZA A

Ginocchio CC, Zhang F, Manji R, Arora S, Bornfreund M, Falk L, et al. **Evaluation of multiple test methods for the detection of the novel 2009 influenza A (H1N1) during the New York City outbreak.** *J Clin Virol.* Jul 2009;45(3):191-195.

(For non-journal subscribers, an additional fee may apply for full text articles.)



[View journal abstract](#)



[View full article](#)

Centers for Disease Control and Prevention (CDC). **Evaluation of rapid influenza diagnostic tests for detection of novel influenza A (H1N1) Virus - United States, 2009.** *MMWR Morb Mortal Wkly Rep.* Aug 7 2009;58(30):826-829.

(For non-journal subscribers, an additional fee may apply for full text articles.)



[View journal abstract](#)



[View full article](#)

Faix DJ, Sherman SS, Waterman SH. **Rapid-test sensitivity for novel swine-origin influenza A (H1N1) virus in humans.** *N Engl J Med.* Aug 13 2009;361(7):728-729.

(For non-journal subscribers, an additional fee may apply for full text articles.)



[View journal abstract](#)



[View full article](#)

Centers for Disease Control and Prevention (CDC). **Performance of rapid influenza diagnostic tests during two school outbreaks of 2009 pandemic influenza A (H1N1) virus infection - Connecticut, 2009.** *MMWR Morb Mortal Wkly Rep.* Sep 25 2009;58(37):1029-1032.

(For non-journal subscribers, an additional fee may apply for full text articles.)



[View journal abstract](#)



[View full article](#)

A number of clinically validated rapid diagnostic tests have been developed for the diagnosis of seasonal influenza. Most of these tests have a sensitivity of approximately 70% but have a specificity of 99% to 100% when used during an influenza season.¹ The sensitivity performance of 70% just about equals that of the clinical assessment using the presence of both a fever and a cough in a patient when influenza is circulating in a community.



How these rapid tests perform in the face of the pandemic H1N1 influenza has been a focus of a number of articles, with some of the data presented in Table 1 below.

Table. Influenza Testing Against Pandemic H1N1 Influenza A Compared to Either Viral Culture or rRT-PCR Assays.^{2,3,4}

Influenza Test	Type	Sensitivity (%)	Specificity (%)
BinaxNow® A&B	Rapid	9.6–40	99.5
Directigen™ EZ A&B	Rapid	21.2–49	99.5
QuickVue™ A&B	Rapid	69	99
Remel Xpect® Flu A&B	Rapid	47	86
Luminex xTag® Respiratory Virus Panel (RVP)	rRT-PCR	97.8	100

rRT-PCR, real-time reverse transcription polymerase chain reaction.

The rapid tests performed better when specimens contained large amounts of virus. On average, rapid tests perform less well against the pandemic strain than against seasonal influenza viruses. Faix and associates examined more than 3000 specimens obtained in April and May 2009 from military individuals and families, and found that the specificity was about 50%, compared with the use of real-time reverse transcription polymerase chain reaction (rRT-PCR).⁵ From these and other data, the positive predictive value of rapid tests tends to be less than optimal, and more importantly, the negative predictive values have ranged between 32% and 75%.⁴ Overall, although rapid tests are easy to perform, their inability to accurately detect H1N1 virus leaves their role as being unsuitable for the evaluation of pandemic H1N1 influenza. Recent recommendations have suggested that rapid influenza diagnostic testing not be relied on for either clinical care or infection control purposes, as these tests are insufficient for securely ruling out pandemic H1N1 infection.⁴ A noted limitation of these studies is that only a relatively small number of patients have been examined, and larger population studies may yield different conclusions.

Virus isolation by culture method is often viewed as the gold standard, but this is labor-intensive and can take days to yield results. rRT-PCR diagnostics offer a quicker and perhaps more definitive determination of infection, with some studies suggesting that the yield may be superior to that of culture assays. In addition, the proprietary Respiratory Virus Panel (RVP) assay offers a broader scope of viral pathogen detection, including influenza A and B, adenovirus, parainfluenza I to III, rhinovirus, metapneumovirus, and respiratory syncytial virus. In the study by Ginocchio and colleagues, the RVP assay detected influenza A viruses in 46.6% of samples, whereas other methods performed less well: rapid antigen tests, 13.7%; direct fluorescent antigen (DFA), 12.1%; and culture, 17.7%.

In a separate article, RVP retrieval of untypeable influenza A virus appears to represent pandemic H1N1 influenza A virus in the current environment.⁶ The US Food and Drug administration has authorized this test for clinical emergency use; it is likely the best test currently available for detecting pandemic H1N1 influenza A virus in <48 hours. Although the RVP assay and similar approaches will play a clear role in the diagnostic evaluation of influenza this year, the test is more labor-intensive and costly than rapid antigen detection tests. Accordingly, efforts to refine these less costly alternatives to enhance detection of novel H1N1 influenza A will be welcomed by clinical laboratories and practitioners, particularly for hospitalized patients.

Key Summary Points

- Novel H1N1 preferentially affects younger age-groups than seasonal influenza
- Compared with seasonal influenza, there is increased transmissibility of the H1N1 virus to susceptible individuals
- Currently available rapid influenza testing poorly detects pandemic H1N1 influenza A virus
- H1N1 influenza case's the overall fatality rate appear to be lower than seasonal influenza rate; however, the H1N1 virus is capable of causing severe disease and mortality in young and previously healthy individuals, although most patients with severe illness have preexisting comorbidities
- Antiviral therapy is advocated only for individuals who are admitted to the hospital or those who have risk factors for severe illness
- Oseltamivir resistance in pandemic H1N1 influenza A virus has been described but appears limited to date

References

1. Hurt AC, Alexander R, Hibbert J, Deed N, Barr IG. [Performance of six influenza rapid tests in detecting human influenza in clinical specimens.](#) *J Clin Virol.* 2007;39(2):132-135.
2. Ginocchio CC, Zhang F, Manji R, Arora S, Bornfreund M, Falk L, et al. [Evaluation of multiple test methods for the detection of the novel 2009 influenza A \(H1N1\) during the New York City outbreak.](#) *J Clin Virol.* 2009;45(3):191-195.
3. Centers for Disease Control and Prevention (CDC). [Evaluation of rapid influenza diagnostic tests for detection of novel influenza A \(H1N1\) Virus - United States, 2009.](#) *MMWR Morb Mortal Wkly Rep.* 2009;58(30):826-829.
4. Centers for Disease Control and Prevention (CDC). [Performance of rapid influenza diagnostic tests during two school outbreaks of 2009 pandemic influenza A \(H1N1\) virus infection - Connecticut, 2009.](#) *MMWR Morb Mortal Wkly Rep.* 2009;58(37):1029-1032.
5. Faix DJ, Sherman SS, Waterman SH. [Rapid-test sensitivity for novel swine-origin influenza A \(H1N1\) virus in humans.](#) *N Engl J Med.* 2009;361(7):728-729.
6. Ginocchio CC, St George K. [Likelihood that an unsubtypeable influenza A virus result obtained with the Luminex xTAG respiratory virus panel is indicative of infection with novel A/H1N1 \(swine-like\) influenza virus.](#) *J Clin Microbiol.* 2009;47(7):2347-2348.

© 2009 JHUSOM and *eInfections Review*

Presented by JHUSOM in collaboration with [DKBmed](#).

COMPLETE THE POST-TEST

Step 1.
Click on link to download instructions for the posttest and evaluation

PHYSICIAN
POST-TEST